14 End-Stage Renal Disease in Patients with Autosomal Dominant Polycystic Kidney Disease

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Incidence and Prevalence of End-Stage Renal Disease

The incident number of individuals with cystic kidney disease reaching end-stage renal disease (ESRD) in the USA has more than doubled from under 1000 in the early 1980s to over 2000 by the early 2000s [1]. Despite this rising number over the past three decades, the proportion of ESRD attributable to ADPKD has been outpaced by the rise in diabetic kidney disease. Thus the overall proportion of ESRD attributable to PKD has steadily declined from 8% in 1980 to slightly under 3% in 2011.

Data from the Danish National Registry reported on 693 patients that reached ESRD with ADPKD between 1990 and 2007. In this population there was an increase in the incidence of ESRD, with 6.45 per million people (pmp) between 1990 and 1995, 7.39 pmp between 1996 and 2001, and 7.59 pmp between 2002 and 2007. In addition, the prevalence of patients with ESRD due to ADPKD also increased across the same time periods, with 55.9, 58.5, and 60.6 pmp, respectively. The age of ESRD onset also increased from 55.9 years in the 1990–1995 cohort to 60.6 years in the 2002–2007 cohort. This suggests that over time, older people with ADPKD were more often being classified with ESRD or initiated renal replacement therapy. It may also suggest that chronic kidney disease care for those with ADPKD has improved over the time, leading to a delay in the onset of ESRD [2]. The male-to-female ratio for the onset of ESRD fell from 1.6 to 1.1, suggesting that male gender was playing less of a role as a prognostic risk factor for progression to ESRD [2].

Survival on dialysis has improved in patients with ADPKD, as compared to non-ADPKD patients [2, 3]. Whether this relates to improved hypertension control, a greater use of angiotensin blocking agents, or other advances in medical management in those with ADPKD remains unclear. Patients with ADPKD have favorable survival on renal replacement therapy compared to similarly matched nondiabetic patients with ESRD [4] (Fig. 14.1). This may be in part due to comorbidities found in patients with ESRD due to hypertension that may not exist in patients that develop ESRD due to a genetic mutation causing ADPKD or because of earlier treatment of hypertension in the ADPKD patient population.

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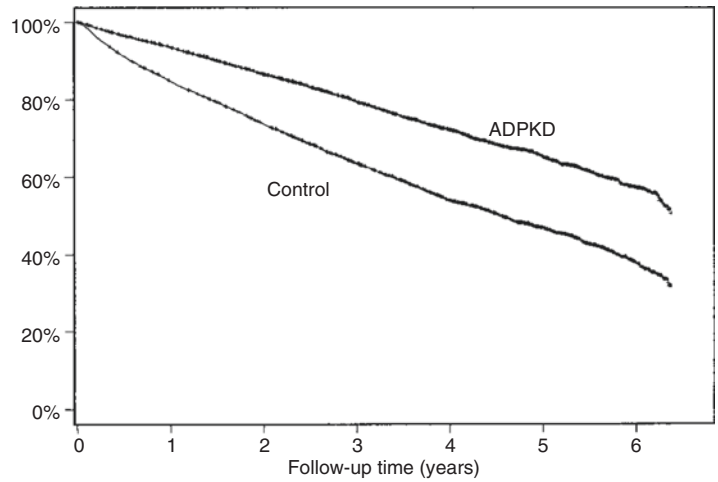

Fig. 14.1 The survival of 9435patients with ADPKD following ESRD, compared with 206,989 age, gender, and year of ESRD-matched nondiabetic controls from USRDS (log rank test $p = 0.0001$) (From Perrone et al. [4]. Reprinted with permission from Elsevier via STM Permissions Guidelines)

Choice of Renal Replacement Therapy

The best choice for renal replacement modality for those with ADPKD is extrapolated from patient outcomes in the general ESRD population. Currently the optimal therapy remains kidney transplantation, and ideally from a living kidney donor, if available [5]. Although kidney transplantation should be recommended as first-line therapy, the patient's preferences, risk profile for infection and malignancy, comorbidities, urgency to initiate renal replacement therapy, social support, and the patient's comprehension of their disease and risks must be kept in perspective.

Despite current efforts to slow cyst growth and GFR decline, almost half of patients with ADPKD reach ESRD by age 60 [6]. Some patients with ADPKD may need to initiate dialysis before kidney transplantation is possible, while some may be ineligible for a transplant. Options for these patients include both hemodialysis (HD, in-center or home-based) and peritoneal dialysis (PD).

Peritoneal Dialysis

Peritoneal dialysis offers a potentially more lifestyle-friendly mode of renal replacement therapy; however, several concerns regarding peritoneal dialysis in ADPKD patients have been raised. The extrarenal manifestations of abdominal wall hernias and leaks are prevalent in those with ADPKD, which would complicate the administration of PD fluid. Another theoretical concern is the higher prevalence of colonic diverticulosis or diverticulitis in patients with ADPKD, which could lead to increased rates of peritonitis. Finally, enlarged polycystic kidneys could restrict the available space to instill PD fluid or restrict the area for peritoneal exchange. Restrictions on the volume of PD fluid infused can result in suboptimal dialysis clearance or patient discomfort with larger volumes. Additionally, there may be an increased concern for hydrothorax with PD. While nephrectomy can offer a possible solution to the lack of intra-abdominal space, the loss of residual kidney function may be a greater concern, as it is known that preserving residual kidney function confers a survival advantage in ESRD patients on PD [7].

Outcomes on PD for patients with ADPKD have been evaluated by several observational and registry studies [8–10]. The US National CAPD Registry reported a median time to peritonitis of 8.2 months in patients with ADPKD, compared to 6.3–7.4 months in other subgroups of kidney failure [11]. Several observational studies comparing patients with ADPKD with matched patients with other causes of ESRD have shown little difference in technique survival or peritonitis

rates [8–10, 12, 13]. In many of these studies, the reported rate of hernias was higher in the ADPKD group.

Registry and cohort studies inherently are at risk of bias, particularly selection bias as patients with ADPKD are directed to PD or HD based on several factors that may be judged to be associated with better success using a particular modality. This is highlighted by examining the competing risks of patients on PD with and without ADPKD. In the French RDPLF peritoneal dialysis registry, 344 patients with ADPKD were compared to 3818 nondiabetic and non-ADPKD patients [12]. The most common outcome for non-ADPKD patients was death, followed by transfer to hemodialysis, and then kidney transplantation. However, in those with ADPKD, the most common outcome was transplantation followed by transfer to hemodialysis and death.

Clinical trials randomizing ADPKD patients to hemodialysis or peritoneal dialysis are unlikely to be conducted. To overcome some of the selection bias of observational studies, a study reported out of Hong Kong is helpful to describe the natural outcomes of ADPKD patients initiated with PD [14]. In Hong Kong, all ESRD patients were assigned to PD first and only switched to HD if there was ultrafiltration or technique failure. Using this mostly unselected population of 42 patients with ADPKD and 84 matched nondiabetic controls, they found no differences in technique or patient survival between the two groups. There was also no significant difference in the transition of patients to hemodialysis. Two urgent surgical hernia repairs did occur in the ADPKD cohort, but all patients resumed PD after recovery with no recurrent hernias.

To date, there is no evidence that specifically correlates total kidney or liver volume with PD success or clinical outcomes in patients with ADPKD. Given the preponderance of clinical studies and reports, it appears that patients with ADPKD can safely and effectively be treated with PD when they reach end-stage renal disease, keeping in mind the potential limitations of this modality.

Hemodialysis

Initiating hemodialysis for ADPKD is generally similar to non-ADPKD patients. Nonetheless, there are some unique issues to be considered in the surveillance and management of patients with ADPKD on hemodialysis.

Renal and Extrarenal Complications

There are limited studies that examine renal and extrarenal complications of ADPKD after initiation of hemodialysis, and most of these come from single-center reports rather than large prospective registries. Renal complications such as pain, hematuria, and renal cyst infections can still occur after ESRD. In cohort studies, symptoms related to these complications vary considerably. After 5 years on hemodialysis, over 50% of patients with ADPKD will experience at least one episode of kidney pain or gross hematuria, while cyst infections will occur in 12% [15]. Although the risk of renal cell carcinoma has not been shown to be increased once on hemodialysis, it is prudent to evaluate cases of gross hematuria, as acquired cystic disease is still a clinical issue in any patient on hemodialysis. Recurrent episodes of hematuria may prompt cessation of heparin anticoagulation on dialysis, addressing coagulopathies, including uremic platelet dysfunction, and finally, when refractory bleeding persists, embolization or nephrectomy of the involved kidney may be a last resort.

Most extrarenal complications have not been reported to be increased after starting dialysis. Cardiac valvular disease, congestive heart failure, valve replacement, and endocarditis are not known to be increased in ADPKD compared to other dialysis patients [15]. An analysis of Medicare patients in the United States Renal Data System (USRDS) showed that the incidence of intracranial hemorrhage was almost threefold higher in those with ADPKD as compared to non-ADPKD, after accounting for competing risks. The absolute risk remained low at 10.9 per 1000 patient-years in those with ADPKD, compared to 7.5 per 1000 patient-years in those

with ESRD due to other causes. Nonetheless, in those with an aneurysm rupture, the death rate was significantly higher. This study could not examine the potential influence of family history or PKD genetics [16].

Anemia Management

It has been hypothesized that expanding cysts within the renal parenchyma leads to pericystic hypoxia, the stimulation of hypoxia-inducible factor-alpha, and eventually resulting in higher endogenous erythropoietin production [17]. Data from nephrectomized ADPKD kidneys have also shown erythropoietin levels to be elevated independent of oxygen tension. Moreover, patients with ADPKD may also start dialysis with more residual kidney function, and thus endogenous erythropoietin production may be higher than for other causes of kidney failure.

Relatively higher hemoglobin values have been frequently observed in ADPKD patients, and this finding may persist even after reaching end-stage renal disease [18]. Moreover, the absence of erythropoiesis-stimulating agent (ESA) therapy is more than five times higher in patients with ADPKD than non-ADPKD patients [19]. In general, ADPKD patients that maintain a higher hemoglobin level do not appear to be at any increased mortality risk, and phlebotomy is not indicated when hemoglobin levels are above the conventional target range for patients treated with ESAs [19].

Hypertension

Hypertension is a common early finding in ADPKD, occurring in 50–70% of cases before any significant reduction in glomerular filtration rate [20]. The stimulation of the renin-angiotensin-aldosterone system, a result of renal parenchymal ischemia caused by cyst expansion, likely plays an integral role in the development of hypertension. As a result, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the mainstay of treatment in these patients [21, 22]. For ADPKD patients specifically on dialysis, there is no further recommendation regarding the preferred antihypertensive agent(s) which should be used.

Among hemodialysis patients, those with ADPKD display a similar U-shaped blood pressure and mortality relationship as those without ADPKD. Despite this hypertension "paradox," which showed that lower blood pressure was associated with higher mortality as compared with normal and higher blood pressure, what is still evident is that the survival in any blood pressure category remained higher for those with ADPKD, as compared to those with other causes of ESRD [23]. Randomized clinical trials are needed to define optimal blood pressure targets in the hemodialysis population.

Mineral Bone Disease

The presence of ADPKD does not appear to modify the association between mineral bone disease markers and mortality in hemodialysis patients. Nonetheless, ADPKD patients with higher levels of mineral bone disease biomarkers still have superior survival to non-ADPKD patients with similar markers [24].

Anticoagulation

Patients with ADPKD on dialysis continue to be at risk for macroscopic hematuria, cyst bleeding, and intracranial aneurysms. However, there are no specific recommendations for modifying the use of systemic anticoagulants for hemodialysis. Should severe or persistent cyst bleeding or macrohematuria occur, it would be prudent to stop systemic anticoagulants and investigate for the underlying cause to guide management.

Kidney Transplantation

Similar to other ESRD patients, the optimal renal replacement therapy option for patients with ADPKD is kidney transplantation. A preemptive kidney transplant, when available, should be the preferred approach. Nonetheless, issues related to the selection of a living donor from the same

family, the indications for native nephrectomy, the choice of immunosuppression, and the elevated risk of certain posttransplant complications should be recognized.

Rates and Prevalence of Kidney Transplantation

Patients with ADPKD represent less than 5% of the total US ESRD population. Similarly, the absolute number of deceased and living donor kidney transplants is also small. However, the rate of kidney transplantation in the USA for those with cystic kidney disease is much higher than any other renal disease (Fig. 14.2). The rate of deceased donor kidney transplantation is approximately 6.4 transplants per 100 dialysis patient-years, compared with 3.7, 2.0, and 2.0 for glomerulonephritis, diabetes, and hypertension, respectively. For living kidney donation, the rate is 4.1 transplants per 100 dialysis patient-years, compared to 2.1, 0.7, and 0.9 for glomerulonephritis, diabetes, and hypertension, respectively. There has been little change in these rates over the past decade in the USA [1].

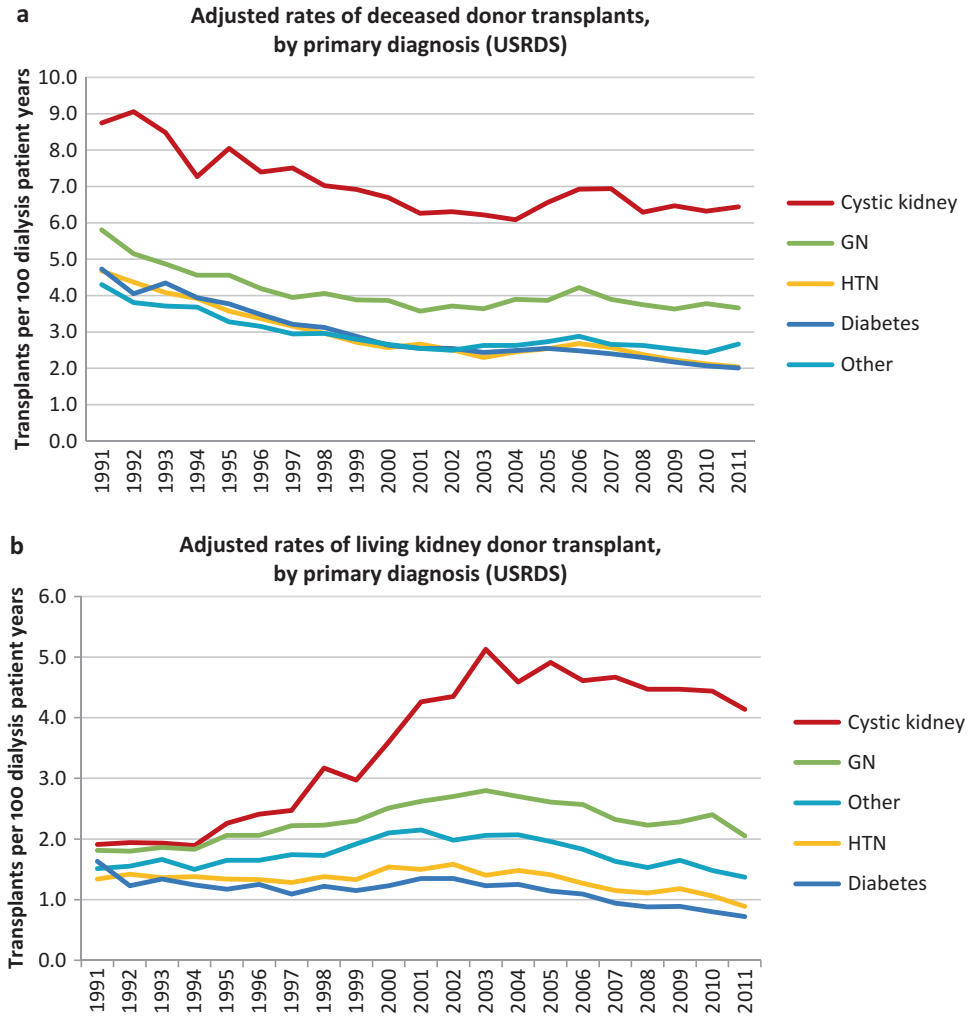

Fig. 14.2 The adjusted rate of kidney transplantation for those with cystic versus other primary diagnoses (**a**) deceased and (**b**) living donors. Adapted from USRDS (Data from United States Renal Data System, 2013 Annual Data Report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014)

The incidence of kidney transplantation in the first year after initiating dialysis is 5% for the total US ESRD population. In those with ADPKD, their incidence of kidney transplantation is as high as 25% in the first year after starting dialysis [25].

Pretransplant Considerations

Alloimmunization

Sensitization to human leukocyte antigen (HLA) can be induced by blood transfusion, prior organ transplantation, and pregnancy. The presence of such HLA antibodies can delay or prevent kidney transplantation [26].

Individuals with ADPKD may manifest gross hematuria from cyst bleeding or rupture, but their need for blood transfusions in this context is extremely uncommon. On the other hand, native nephrectomy of massively enlarged or recurrently bleeding and infected ADPKD kidneys may significantly raise the risk of requiring a blood transfusion. In addition, declining GFR is associated with anemia, yet this appears to be less of an issue in those with ADPKD, and management is driven mainly by erythropoiesis-stimulating agents and iron supplementation.

To minimize alloimmunization, the avoidance of blood transfusions should be encouraged, similar to non-ADPKD patients. Specifically, the benefits of native nephrectomy should be balanced with risks, including that of sensitization from transfusion. The use of blood transfusions should be limited to urgent and lifesaving indications.

Aneurysm Screening

The rupture of an intracranial aneurysm portends a severe prognosis. As kidney transplantation involves the use of a scarce and precious resource, namely, a kidney from a deceased or living donor, some transplant centers advocate for screening of ADPKD patients for occult intracranial aneurysms. The rationale is that this approach would allow for preemptive management of unruptured aneurysms, which would avoid rupture and thus improve morbidity and premature mortality of the transplant recipient and maximize the use of the allograft. There are, however, no studies that specifically examine the utility of screening asymptomatic patients with ADPKD for intracranial aneurysms prior to kidney transplantation. Screening for intracranial aneurysms is traditionally indicated for those with symptoms compatible with an aneurysm or in the context of a family history of ruptured aneurysm, subarachnoid hemorrhage, unexplained stroke, or premature death. Widespread screening of asymptomatic patients with ADPKD is not supported [27].

Living Kidney Donation

Kidney transplantation from a living donor allows for several potential advantages: eliminating the need for dialysis (preemptive transplantation), providing the recipient the opportunity to plan for the transplant as an elective procedure, offering improved short-term and long-term graft survival, and shortening the wait time for patients on the deceased donor wait-list.

A clear challenge for patients with ADPKD is finding a kidney donor among family members, given the genetic nature of the disease. An autosomal dominant disease implies that statistically there is a 50% chance that each sibling or child of that potential recipient also carries the genetic mutation, thus excluding any affected family members and reducing the available donor pool. With multiple potential recipients in a family, this further raises the demands on any healthy donors.

In potential donors from ADPKD families where there may be no apparent evidence of cystic disease by ultrasonography, the exclusion of the disease may be reliably concluded in those above age 40 [28]. In younger potential donors, the diagnosis is more difficult to exclude with sufficient certainty. In this setting, further evaluation with higher resolution imaging of cysts (i.e., MRI) or genetic testing is appropriate [29] (see

also Chaps. 1 and 7). If a mutation in the recipient has been characterized, a familial mutation analysis may be performed. When no mutation in the family has been identified, the alternative is to perform full gene sequencing of both *PKD1* and *PKD2* genes in the potential donor to help exclude the disease.

Eligible candidates that are blood type or crossmatch incompatible with their intended recipient may still have the opportunity to enter into a living donor paired-exchange program, if available in their country or region. These programs increase the chance of recipients finding a compatible kidney donor and can match two pairs, or they may create a chain of many donor-recipient pairs. Patients with ADPKD can be informed of this potential approach, as it still offers all the advantages of living kidney donation.

Native Nephrectomy

As total kidney volume increases with disease progression, patients may develop more and increasingly severe symptoms. The indications for native kidney nephrectomy are driven by symptoms: chronic pain, early satiety symptoms, chronic or refractory cyst infections, recurrent hematuria or suspicion of malignancy, recurrent nephrolithiasis, and, rarely, refractory hypertension. As previously mentioned, the decision to intervene with nephrectomy should be balanced by the risks for transfusion requirements in a potential kidney transplant candidate.

Prior to kidney transplantation, the presence of massively enlarged polycystic kidneys may provide another indication for ipsilateral native nephrectomy. This would be to provide adequate space for the surgical implantation of the renal allograft.

Several approaches are available for the removal of native kidneys peri-transplant and each with its own potential advantages and disadvantages. Nephrectomy can be performed using laparoscopic techniques. Bilateral nephrectomy pretransplant may be indicated in extreme circumstances and would preclude avoiding dialysis. This approach would also lead to the complete loss of urine output (residual kidney function), which is valuable for those on dialysis. Finally, the more extensive and complicated the surgery, the more risk of requiring a blood transfusion. However, the removal of the native kidneys allows for adequate space for the allograft and no concern for future kidney surgery in an immunosuppressed patient.

For asymptomatic patients, a simultaneous ipsilateral nephrectomy is sometimes performed to allow for space for the transplant allograft. This technique allows for a single surgery, which is associated with shorter cumulative hospital stays and better patient satisfaction. The combined nephrectomy and transplant surgery does lead to a longer and more complicated procedure, with the potential for a longer cold ischemia time in deceased donor transplants. There have also been reports of greater transfusion requirements. Published reports have not shown any significant differences in allograft function when comparing staged or simultaneous nephrectomy and those without.

Finally, a staged nephrectomy (also known as deferred or sandwich nephrectomy) begins with a simultaneous nephrectomy, and once the transplant is successful, a contralateral nephrectomy is performed. This does require an additional surgery but allows for the kidney function and immunosuppression to stabilize posttransplant.

Several studies have reported on their success of pretransplant and simultaneous nephrectomy compared to transplant without nephrectomy and unilateral versus bilateral nephrectomy. The majority of these reports are retrospective reviews involving single centers and often with individual surgeons [30, 31]. A comparison of transplant compared to transplant with ipsilateral nephrectomy showed no difference in intraoperative or postoperative complications, including no increased length of stay or blood loss. The largest report involved the routine approach of simultaneous nephrectomy in all ADPKD transplant patients [32]. In 100 consecutive kidney transplant recipients, 22 surgical complications were documented, with 12 complications attributed to the additional nephrectomy: 4 lymphocele, 4 wound dehiscence or

hernia, and 4 postoperative hematomas or bleeding. Of these 100 patients, 22 had previously undergone a contralateral nephrectomy. Of the remaining 78 patients, 20 underwent contralateral nephrectomy subsequent to their transplant. The overall 1- and 5-year patient survival was 97% and 93%, and 1- and 5-year graft survival was 96% and 80% [32]. As there were no concomitant controls available at this center, it is unclear how these result compare to alternative strategies, and the indication for nephrectomy was not based on clinical indications as demonstrated by the fact that some kidneys were as small as 500 g in weight.

Separate studies comparing simultaneous with staged nephrectomy showed a longer cumulative operative time, greater blood loss and transfusion requirements, and longer hospital stay in those with the staged bilateral nephrectomy; however postoperative short-term graft function and 5-year graft and patient survival were similar in both groups [31, 33, 34].

Overall, it is difficult to conclude the true impact of native nephrectomy in asymptomatic ADPKD patients, as the data is based on case series, and there are no randomized trials. In the hands of experienced transplant centers and surgeons with the appropriate expertise, the outcomes of native nephrectomy, whether unilateral or bilateral, may not impact intermediate-term graft and patient outcomes. However, keeping the native kidneys in situ, if possible, would avoid the inherent complexity of performing any additional surgery, and thus minimize the risk for blood transfusion and sensitization, and maintaining residual renal function, which could simplify fluid management and preserve erythropoietin production [35]. There is insufficient evidence to support routine nephrectomy, and it should probably be restricted to centers with experience in performing the procedure safely.

Posttransplant Considerations

What happens to symptom evolution and total kidney volume after transplantation is not clearly understood. Data examining 33 patients that were followed by CT imaging at the time of transplant and then 1, 3, and 5 years posttransplant reported on the rate of kidney volume change [36]. In this cohort, the mean bilateral kidney volume at the time of transplant was 3100 mL, all but one had basiliximab induction, all patients received calcineurin inhibitors and prednisone, and over 85% received mycophenolate mofetil. All but one patient experienced a decrease in kidney volume after transplantation, with an average decrease of 37.7% at 1 year and 40.6% at 3 years. Interestingly, the majority of the decline was observed in the first year after transplant. Also, in 16 of 18 patients with a polycystic liver, there was an increase in liver volume. These results provide an argument against pretransplant nephrectomy in the absence of infection, bleeding, malignancy, or inadequate room for the allograft. It does highlight the possibility of increasing liver-related symptoms after transplant.

Choice of Immunosuppression

In animal models of ADPKD, the inhibition of the mammalian target of rapamycin (mTOR) was shown to slow disease progression [37, 38]. This observation was further supported in retrospective studies of transplanted patients with ADPKD. A retrospective review of kidney transplants for ADPKD at the Cleveland Clinic identified seven patients with CT scans in the pre- and posttransplant period and classified these into sirolimus and non-sirolimus treatment [39]. It was determined that the total kidney volume change was $-24.8 \pm 9.7\%$ (-1.4% per month) in those on sirolimus and $-8.6 \pm 11.2\%$ (-0.3% per month) in the non-sirolimus treatment group. A similar phenomenon was described with polycystic liver volume [40]. In 16 patients with abdominal imaging studies within 11 months before and 7 months after transplantation, sirolimus was associated with a 11.9% decrease in liver volume, while there was a 14.1% increase for those treated with tacrolimus.

Since these observations, randomized clinical trials in non-transplant patients with ADPKD

have not demonstrated slowing of kidney volume progression or slowing of renal impairment in those treated with mTOR inhibitors [41, 42]. In addition, there is also the possibility that native cyst growth may slow simply from the fibrosis associated with calcineurin inhibitors.

Currently, no specific recommendations can be made that relate to the choice of immunosuppression in patients with ADPKD. As with any transplant recipient, the primary objectives should be to prevent graft rejection and avoid complications of over-immunosuppression to ensure optimal long-term graft and patient survival.

Liver and Kidney Transplantation

Liver involvement is one of the most common extrarenal manifestations in ADPKD. The majority of ADPKD patients do not develop symptoms related to liver cystic disease. Occasionally, congenital hepatic fibrosis and biliary tract dilatation can manifest, but most commonly symptoms relate to progressive enlargement of a polycystic liver. Hepatocellular function, however, most often remains preserved. Women are more likely to develop cystic liver involvement, and the number of cysts has been correlated to estrogen use and number of pregnancies [43]. A massively enlarged polycystic liver can result in chronic symptoms of abdominal fullness and pain. Early satiety and dyspnea can result from mechanical compression and displacement of the adjacent organs. Eventually the chronic liver enlargement can become physically disabling and even lead to malnutrition and severely impaired quality of life.

Orthotopic liver transplantation has been performed in patients with ADPKD in the absence of renal dysfunction. When surgical liver resection is unsuccessful or not feasible, liver transplantation can be considered in the context of disabling symptoms, portal hypertension, or liver dysfunction and optimally before physical function significantly deteriorates. One-year mortality following liver or liver-kidney transplantation in patients with ADPKD has been estimated to be 18% [44].

Similar to patients without ADPKD, isolated liver transplantation has been associated with an early decline in GFR. Summarizing data from various case series, it is reported that the mean GFR decline is 15 ml/min per year. This rate of GFR decline is faster than that expected from ADPKD alone and is likely a result of the use of calcineurin inhibitors. Regardless, a strategy of combined liver-kidney transplantation prior to kidney failure is not supported, and the monitoring of kidney allograft GFR and rejection are generally confounded when residual native kidney function is still present [44].

Posttransplant Complications

Certain complications are increased in those with ADPKD compared to non-ADPKD controls posttransplant, and there is significant heterogeneity in the reports from different case series and longitudinal studies. Urinary tract infections have been reported to be increased as much as twofold in ADPKD patients, although some longitudinal studies find little evidence of any increased infection risk [45, 46]. Similarly, colonic diverticulitis has also been reported to be more prevalent and rarely associated with life-threatening bowel perforation.

In all kidney transplant recipients, cardiovascular disease remains the major complication affecting patient outcomes. Preventing or treating factors that elevate cardiovascular risk should be an important objective in transplant patient care. The largest multicenter longitudinal cohort study (DIVAT) followed 534 ADPKD patients for 15 years after kidney transplant. Hypertension (49.7% vs. 42.3%) and hyperlipidemia (49.7% vs. 39.3%) were significantly more prevalent in patients with ADPKD. New-onset diabetes after transplant was also more likely (12.4% vs 9.6%, $p = 0.06$). Nevertheless, patient survival and the incidence of stroke were no different in those with and without ADPKD [46].

Another potential concern has been the incidence of cerebrovascular and thromboembolic disease. Several longitudinal cohort studies, examining cerebrovascular events among ADPKD patients following kidney transplant, have not shown any increased risk of stroke. Although there was an increase in hemorrhagic bleeds in univariate analysis, this was subsequently accounted for by underlying risk factors in multivariate analyses [45–47]. The Assessment of Lescol in Renal Transplantation (ALERT) study was a randomized, double blind clinical trial examining fluvastatin in kidney transplant recipients [48]. Of the 2102 patients included in the analysis of cerebrovascular disease and mortality, 321 had ADPKD as their primary cause of kidney failure. This study showed that 8.8% of the population experienced a cerebrovascular event over the 6.7-year median follow-up (i.e., incidence rate of 1.3% events per year), and ADPKD was an independent risk factor for hemorrhagic stroke, but not ischemic stroke, with over a fourfold increase in hazard ratio [48]. With respect to venous thromboembolic disease, the DIVAT study was a multicenter cohort study in France, which demonstrated an incidence of thromboembolic disease of 8.6% in those ADPKD compared to 5.8% in the control population ($p = 0.009$) [46].

Posttransplant malignancy has not been found to be increased in patients with ADPKD [49]. Specifically, renal cell cancers and other solid organ tumors do not appear to be more prevalent compared to other transplant recipients [46, 50]. Since malignancy risk may be increased in general for kidney transplant recipients and kidney cancer is increased for those with prolonged dialysis duration, attention to periodic cancer screening and general preventative measures should be no different in those with ADPKD. The largest registry study using data from the Scientific Registry of Transplant Recipients (SRTR) found that the adjusted cancer risk was 16% lower in ADPKD patients when compared to the general population. Specifically, renal cell carcinomas showed no increased incidence rate (89.2 vs. 106.0 per 100,000 person-years) [51].

ADPKD in a Transplanted Kidney

Recurrence of cystic disease in a transplanted kidney is never observed. However, kidneys have been transplanted from ADPKD donors. Progression of cyst and total kidney volume expansion has been demonstrated in these kidneys; however, these allografts can still last for many years with adequate GFR [52]. The question of whether kidneys from deceased ADPKD donors with acceptable kidney function and normal size may be appropriate for transplantation requires the full consent of the potential recipient, but may be considered by some programs.

Patient and Graft Survival

Kidney transplantation in patients with ADPKD yields favorable patient outcomes that are comparable to similar (nondiabetic) ESRD patient populations and are likely better than those with diabetic kidney disease [4, 50]. The DIVAT study also found that death-censored graft survival was higher in ADPKD patients. This was in spite of the ADPKD patients in their registry receiving kidneys from older donors with a higher prevalence of cardiovascular disease, having a lower proportion of living kidney donors, and having longer cold ischemia time [46]. The largest study of ADPKD patients posttransplant ($N = 3170$) compared to nondiabetic controls ($N = 1554$) found a difference in the overall survival between the groups [4] (Fig. 14.3).

Conclusion

Autosomal dominant PKD leads to kidney failure in many affected individuals. Their management after reaching ESRD remains challenging, particularly given the lack of disease-specific management options. Nonetheless, the outcomes of these individuals are favorable both on dialysis and with kidney transplantation.

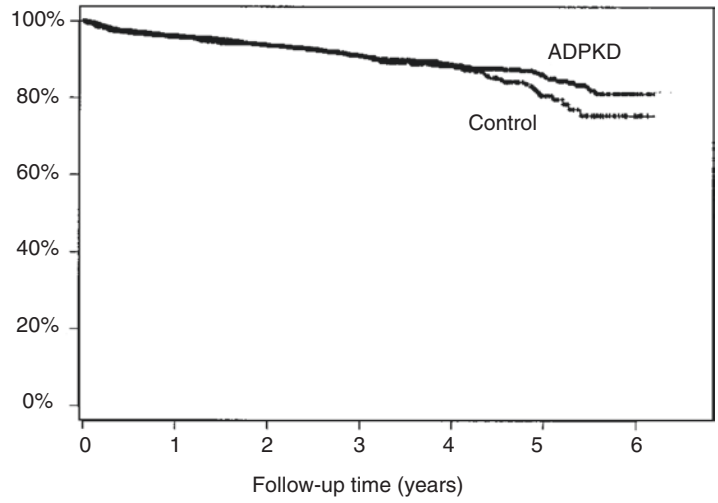

Fig. 14.3 The survival of 3170 patients with ADPKD following kidney transplantation, compared with 1554 nondiabetic controls from USRDS (log rank test $p = 0.23$) (From Perrone et al. [4]. Reprinted with permission from Elsevier via STM Permissions Guidelines)

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